

**REMARKS**

Upon entry of this amendment, claims 1-3, 5-6, 9, and 14-16 will be amended. Claims 4 and 7-8 are canceled. Claims 9-16 are withdrawn as being directed to a non-elected invention. Claims 1-3, and 5-6 are all the pending claims that are being examined in this application.

The Office Action makes of record the telephone restriction requirement and applicants' election of the invention of Group I, claims 1 to 8, directed to compounds where i is 0. The Office Action states that Applicants should affirm this election when responding to the Office Action. Applicants hereby affirm this election.

Applicants have amended claims 1 to 3 to direct them to the elected invention.

Further, Applicants request that claims 9-16 to be rejoined should any of the elected claims be found to be allowable or upon allowance of the elected claims.

Claim 1-8 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Office Action asserts that the recitation "tetrahydroquinoline derivative" is not clear as to what other derivatives could be included other than that encompassed by formula I.

The Office Action also asserts that the claims have too many brackets that makes the claims confusing as to what groups are drawn to which formula.

In response, Applicants submit that the claims pending prior to this amendment clearly define what Applicants regard as the claimed invention. However, solely to advance prosecution of the present application, Applicants have amended the claims to remove the term "derivative" and to remove the brackets.

Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

Claims 1-8 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for  $R^2$  to be a phenyl, pyridyl and furan, and  $C\equiv C$ - alkyl, and compounds as given in table 1, does not reasonably provide enablement for  $R^2$  to be any hetero. The Office Action asserts that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In response, Applicants have amended claim 1 to incorporate the recitations of  $R^2$  that appeared in original claim 5, that is, a phenyl group having  $R^4$  at the 4-position or a 6-membered heteroaryl group having  $R^4$  at the 4-position.

As recognized by the Examiner, the specification provides enablement for  $R^2$  being phenyl and pyridyl, which is a 6-membered heteroaryl group. The specification, at page 12, lines 16-23 and page 16, lines 6-11 discloses various pyridyl groups and a 2-pyrazinyl group as examples of a 6-membered heteroaryl group, and Table 1 discloses working examples of various compounds containing pyridyl groups.

Applicants submit that the present specification, including the working examples of the compounds wherein  $R^2$  is a pyridyl group, is sufficient to enable the presently claimed compounds wherein  $R^2$  is a 6-membered heteroaryl group, without undue experimentation.

Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 1-8 have been rejected under 35 U.S.C. § 103(a) as being obvious over WO 01/27086 to Hanada et al. (April 2001; hereinafter "the '086 application"). The corresponding

U.S. Patent No. 7,037,919 to Hanada et al. (hereinafter “the ‘919 patent”) is relied on as an English equivalent of the ‘086 application.

The Office Action asserts that the claimed tetrahydroquinoline compound represented by Formula (I) in which i is 0 is disclosed by the ‘086 application. The Office Action asserts that the “only difference between the compounds of the prior art and [Applicants’] is the double bond in [the] 5[-]membered ring” and that a species with a double or single bond is taught in the ‘086 application. (See Table 9 of the ‘086 application).

The Office Action asserts that one of skill in the art would have been motivated by the ‘086 application to make the claimed compounds which do not have the double bond in the 5-membered ring, and expect it to retain its properties, so that it would be prima-facie obvious to make the compounds of the claimed invention.

The Office Action states that the ‘086 application is prior art only under 35 U.S.C. §102(e). However, the ‘086 application was published April 19, 2001, which is more than 1 year prior to Applicants’ August 1, 2003, effective filing date. Therefore, the ‘086 application is legally effective prior art under 35 U.S.C. §102(b) and cannot be removed as a reference.

Applicants note that the following analysis is based on the ‘919 patent, which is the English translation of the ‘086 application.

The ‘919 patent is directed to tetrahydroquinoline derivatives having a general formula (I). (See abstract of ‘919 patent). The tetrahydroquinoline derivatives of the ‘919 patent are disclosed to possess high binding affinity to androgen receptors and exhibit androgen receptor agonism or antagonism. (See abstract of the ‘919 patent).

The presently claimed compounds are compounds in which the ring condensed with the tetrahydroquinoline moiety is saturated, and R<sup>2</sup> is a phenyl group having R<sup>4</sup> at 4-position or a 6-

membered heteroaryl group having  $R^{4'}$  at 4-position, wherein  $R^4$  and  $R^{4'}$  are independently represent a halogen atom,  $-O-R^{5A}$ , or  $-NHCO-R^{5A}$ , wherein  $R^{5A}$  represents a hydrogen atom, or an alkyl group having 1-6 carbon atoms which may be substituted by a fluorine atom.

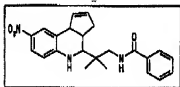
On the other hand, the '919 patent discloses compounds which cover a broad scope of structurally divergent compounds. However, all the species disclosed in the '919 patent have the ring condensed with the tetrahydroquinoline moiety being unsaturated with a double bond.

In addition, the '919 patent does not specifically disclose a substituted phenyl or a substituted 6-membered heteroaryl group as a substituent corresponding to  $R^2$ . The '919 patent neither teaches nor suggests the compounds claimed in the present application which have the characteristic structure as discussed above.

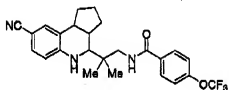
The presently claimed compounds are novel nonsteroidal compounds that do not exhibit excessive action on the prostate, but exhibit strong androgen receptor agonistic action, particularly on bone tissue and skeletal muscle tissue. See the Test Examples in the specification.

Further, as demonstrated in the Rule 132 Declaration submitted herewith, the presently claimed compounds have unexpected androgen receptor agonistic action over the compounds disclosed in the '919 patent. The present inventors determined the androgen receptor agonistic action of the compound disclosed in the '919 patent, which is structurally closest to the presently claimed compounds in the attached Rule 132 Declaration.

Applicants used the compound of Example 56 in the '919 patent as the test compound, represented by the following formula:



which is structurally closest to the compound of Example 1 in the present application, represented by the following formula:



As disclosed in the present specification, Test Example 2 shows that the compound of Example 1 exerted no excessive action on the prostate, and a strong androgen receptor agonistic action on levator ani muscle and bone mineral density. See Table 4 of the present specification which is partially reproduced below.

Table 4

Test compound	Prostate weight (mg/100 g body weight)	Femoral bone mineral density (mg/cm <sup>2</sup> )	Levator ani muscle weight (mg/100g body weight)
Sham control group	94±17	140±16	53±4
ORX control group	8±1	128±4	35±4
ORX+Example 1. 30 mg/kg	70±13**	137±10**	60±6**

Mean±SD \*p<0.05, \*\*p<0.01 on Dunnett's t-test.

In the attached Rule 132 Declaration, the same experiment as that disclosed in Test Example 2 of the specification was conducted except with the compound of Example 56 disclosed in the '919 patent in an amount of 60 mg/kg, which is twice the amount used for the compound of Example 1.

As shown in the figures attached to the Declaration, the compound of Example 56 disclosed in the '919 patent did not show a significant androgen receptor agonistic action on bone mineral density, even in an amount of 60 mg/kg.

Therefore, the presently claimed compounds provide unexpected results that are superior over the compounds disclosed in the '919 patent because the presently claimed compounds demonstrate a strong androgen receptor agonistic action on levator ani muscle and bone mineral density when used in an amount that is half of the amount used for the compound of Example 56 disclosed in the '919 patent.

In conclusion, the '919 patent neither teaches nor suggests the characteristic structure of the presently claimed compounds. Also, the presently claimed compounds have unexpected effects that are superior over the compounds disclosed in the '919 patent and are thus not obvious.

Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 1-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of the '919 patent. The Office Action asserts that even though the conflicting claims are not identical, the claims are not patentably distinct from each other because the '919 patent teaches a genus that encompasses the genus of the claimed invention.

In response, and for at least the reasons discussed above under the section addressing the §103(a) rejection, Applicants submit that the present claims are patentably distinct from the claims of the '919 patent.

**CONCLUSION**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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**23373**

CUSTOMER NUMBER

Date: November 6, 2007